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DEVELOPMENT AND VALIDATION OF UV-SPECTROSCOPY ANALYTICAL METHOD FOR ESTIMATION OF LAFUTIDINE IN SOLID NANO-DISPERSION

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Abstract

The aim of current research is development and validation of straightforward and cost-effective UV spectrophotometer analytical method for detection and quantitative analysis of Lafutidine (LFD) in poloxamer 407 and polyvinyl pyrollidone K-30 solid nano-dispersion. Poloxamer 407 and polyvinyl pyrollidone K-30 based solid nano-dispersion of Lafutidine was fabricated by solvent evaporation method. Regression equation obtained from calibration curve was y= 0.02065x+0.01045. Developed analytical method for LFD showed linearity with high regression coefficient of 0.998 with *p*-value <0.0001. Mean percentage recovery was found in accepted limit of 98-102% which validated the accuracy of the method. Method exhibited specificity, robustness, intra-day and intermediate precision as demonstrated by relative standard deviation of RSD <2%. Limit of detection and limit of quantification of LFD were found 1.96 and 5.96 µg/ml, respectively. It was accomplished that developed UV spectrophotometer technique could be implemented for quantitative estimation of LFD in poloxamer 407 and polyvinyl pyrollidone K30 based solid nano-dispersion formulation.

***Keywords*:** Limit of Detection, Limit of Quantification, Lafutidine, Specificity, Robustness

Introduction

Analytical validation can be described as the compilation and assessment of data obtained by the process / mechanism used to produce a product, whether it is an industrial, laboratory or experimental research. Analytical validation provides scientific proof that using proven and agreed methods, a process reliably produces reproducible, reliable, and accurate findings. Analytical validation consists of several phases, and ends with a master plan for validation. The analytical system validation procedure is followed to ensure that the analytical technique implemented for a specific study satisfies the expected specifications. Guidelines from the International Conference on Harmonization (ICH) and U.S. Food and Drug Administration (USFDA) will offer a basis for pharmaceutical process validations (Carr and Wahlichs, 1990; ICH Q2 R1; Orr *et al.,* 2003; USFDA guidelines, 2015).

The analytical method validation had been executed according to the guidelines of ICH Q2 (R1) for linearity, scale, precision, accuracy, detection limit, and quantification limit. Lafutidine is 2-[(2-furylmethyl)sulfinyl]-N-(2Z-4-{[4-(piperridin-1yl methyl) pyridin-2-yl]oxy}but-2-en-1-yl) acetamide. This helps to antagonize the reaction mediated by the H2 receptor. It is protective against lesions of the esophagus caused by acid reflux by inhibiting acid secretion (Jadhav *et al.,* 2013; Kumar *et al.,* 2017). Lafutidine (LFD) is yellowish white crystalline powder having λ_{max} of 286 nm and Beer-Lambert range of 5-30 µg/ml. The literature showed that different analytical approaches have been identified for the analysis of LFD (Table 1). Ultraviolet (UV) spectrophotometer analytical procedure for the evaluation of LFD in poloxamer 407 and polyvinyl pyrollidone K-30 (PVP K-30) based solid nano-dispersion based has not been reported yet. Hence, for the identification and quantitative study of LFD in solid nano-dispersion (LFD-SND), an innovative and inexpensive UV spectrophotometer analytical procedure has been established. The analytical method was validated for several analytical parameters (Grewal *et al*., 2020; ICH Guideline, 2005; Sharma *et al.,* 2017, Singh *et al.,* 2016; Singh *et al*., 2020).

Table 1 : Assessment of currently established methodological approaches.

Drug	Method	λ_{max} (nm) (Solvent)	LOD/LOQ (µg/ml)	Range* (µg/ml)	Reference
Lafutidine (LFD) Domperidone (DOM)	RP-HPLC	Methanol 268-278 (LFD) 282-292 (DOM)	0.6440/1.9515 (LFD) 0.8029/2.433 (DOM)	-	Rana *et al.,* 2012
Lafutidine	Ultraviolet Spectroscopy	200-400 (Methanol)	3.28/9.95	10-50	Jadhav *et al.,* 2011
Lafutidine and Rabeprazole Sodium (RBZ)	RP-HPLC	215 (Methanol: 20 mM Phosphate buffer: acetonitrile)	2.08/6.3 (LFD) 3.0/9.09 (RBZ)	40-120 (LFD) 80-240 (RBZ)	Antala *et al.,* 2013
Lafutidine	Ultraviolet Spectroscopy	290 (0.1N HCl)	0.545/1.654	1-30	Kumar *et al.,* 2017
Lafutidine	Spectro-florimetric	330 /640	0.048383/ 0.146616	0.5-10	Patel *et al.,* 2013
Lafutidine	HPTLC-densitometric method	190-400 (methanol)	11.4 ng/ml 33.83 ng/ml	100-500 ng /ml	Dhamecha *et al.,* 2013

Lafutidine and domperidone	Derivative Spectrophotometer	258 (LFD) 299 (DOM)	0.5234/2.1215 (LFD) 0.7489/3.0253 (DOM)	2-10 (LFD) 3-30 (DOM)	Moon *et al.,* 2012
Lafutidine and domperidone	Ultraviolet Spectroscopy	279 (LFD) 284 (DOM)	2.08/6.11 (LFD) 0.479/1.45 (DOM)	10-100 (LFD) 5-40 (DOM)	Jadhav *et al.,* 2012
Lafutidine	LC-ESI-MS	287	1 ng/ml/5 ng/ml	5-400 ng/ml	Wu *et al.,* 2005
Lafutidine	RP-UPLC	276 (Acetonitrile)	0.75/1.2	-	Joshi *et al.,* 2013

*Beer-Lambert range; RP-HPLC: Reversed phase high-performance liquid chromatography; HPTLC: High-performance thin layer chromatography; RP-UPLC: Reversed phase ultra-performance liquid chromatography; LC-ESI-MS: Liquid chromatography electro-spray ionization mass spectrometry.

Materials and Methods

Instruments

Double beam scanning UV-Spectrophotometer (Systronics AU-2701, Ahmedabad, India) and (Systronics 2202, Ahmedabad, India) with 1 cm matched quartz cells coupled to computer with UV-Probe software was utilized for measuring absorbance. Digital pH meters (Deluxe model 101, Ambala, India) and an electronic analytical weighing balance (0.1 mg sensitivity, Denver Instrument SI-234, Ambala, India) were utilized during analytical work.

Reagents and Chemicals

Lafutidine (CAS NO- 118288-08-7) was purchased from Yarrow Chem, Mumbai. Poloxamer 407 was purchased from Sigma Aldrich. PVP K-30, potassium dihydrogen phosphate and sodium hydroxide were procured from Loba Chemicals Private Limited, Mumbai (India). All used materials were of analytical standard.

Fabrication of Poloxamer 407 and PVP K30 based Solid Nano-dispersion (SND) of LFD

LFD-SND was manufactured by solvent evaporation technique. LFD was dissolved in methanol (organic phase) while polymers *i.e.* poloxamer 407 and PVP K-30 were dissolved in aqueous phase. Organic phase was slowly added to aqueous phase with continuous mechanical stirring for 30 min followed by evaporation using rotary evaporator to obtain dry LFD-SND powder (Chu *et al.,* 2007, Nkansah *et al.,* 2013; Sarkar *et al.,* 2006; Silva-Buzanello *et al.,* 2015).

Method Development

Preparation of stock and working standard solution

100 mg of LFD was measured precisely and diluted in 100 ml of phosphate solution, pH 6.8 (PB-6.8) in a volumetric flask to produce 1000 µg/ml standard stock solution. 10 ml solution was withdrawn and diluted to 100 ml with PB-6.8 to give 100 µg/ml operational regular solutions.

Determination of Absorption maxima (λ_{max}) and calibration curve of LFD

A working standard solutions of LFD (100 µg/ml) was scanned over an UV spectroscopic scanning range (200-400 nm) using PB-6.8 as blank to determine λ_{max} for LFD. From 100 µg/ml standard stock solution, aliquots (*i.e.* 0.5, 1, 1.5, 2, 2.5, and 3 ml) were diluted to 10 ml dilutions having 5-30 µg/ml concentration and analyzed for absorbance.

Analytical method validation

As per the ICH guidance, analytical parameters like linearity, accuracy, reliability, robustness, precision, detection limit, and quantification limit were tested. The ultraviolet visible spectrometer (Systronics AU-2701, Ahmedabad, India) was used to develop methods with a spectral bandwidth of 1 nm.

Linearity

The analytical protocol linearity was performed in PB-6.8 at six separate concentrations (5, 10, 15, 20, 25, and 30 µg / ml) of LFD. The experiment was conducted in triplicate (total n=9) for three days. The data collected were used to map the linearity curve, equation of regression and equation of the coefficient of correlation. The proposed UV method's limit of detection (LOD) and limit of quantification (LOQ) was created. The LOD and LOQ were determined using the standard reaction deviation and the corresponding curve slope using the appropriate equations:

$$LOD = 3.\frac{3\sigma}{S} \quad ...(4)$$

$$LOQ = \frac{10\sigma}{S} \quad ... (5)$$

Where; 'σ' represents the standard deviation of absorbance of sample and S represents the slope of the calibration curve (Grewal *et al.,* 2020; Sharma *et al.,* 2017, Singh *et al.,* 2016; Singh *et al.,* 2020; Sarkar *et al.,* 2006; Silva-Buzanello *et al*., 2015).

Accuracy

Accuracy is characterized as the proximity of agreement between the true value and the analytical value. Using the standard form of addition, a specified volume of regular stock solution was applied to the pre-analyzed LFD solution at different levels of 100-500 per cent. The suggested approach was used to analyze the solutions. The concentration of the samples was recalculated in triplicate using the linearity curve (Davidson *et al*., Grewal *et al*., 2020; 2002; Kadam *et al*., 2013; Singh *et al*., 2020).

Specificity

Specificity is the capacity to test the analyte unambiguously in the presence of components that would be known to occur. 10 mg of LFD was mixed with 100% (10 mg), 200% (20 mg), 300% (30 mg), 400% (40 mg) and 500% (50 mg) of excipients (PVP K-30 and Poloxamer 407) and analyzed for % recovery of LFD. The accepted limits of recovery and % relative standard deviation (% RSD) for validating specificity are 98-102% and <2, respectively (Abdelwahab *et al.,* 2012; Divya *et al.,* 2014; Maleque *et al.,* 2012; Sarkar *et al.,* 2006; Silva-Buzanello *et al.,* 2015).

Repeatability

It is defined as that under a short period of time precision expresses under the same operating circumstances. Repeatability is also labeled intra-assay precision.

Ascertaining LFD absorbance in PB-6.8 at a concentration of 10, 15, 20 µg/ml measured the repeatability of the UV procedure. The absorbance was measured three times within a day (Alamri *et al.,* 2016; Divya *et al.,* 2013, Prashant *et al.,* 2013).

Intermediate precision

Intermediate precision reflects differences inside laboratories: different days, different researchers, diverse equipment (Breier *et al.,* 2007, Jain *et al.,* 2013). Inter-day precision was determined by analyzing 5, 10, 15µg/ml concentrations of LFD on three dissimilar days (% RSD limit: < 2%). To analyze the effect of varying analyst and equipments, 15µg/ml LFD was analyzed six times (n=6).

Robustness

The robustness of an analytical technique is an indicator of its ability to remain unchanged by limited, yet deliberate changes in process parameters and demonstrates its reliability during daily use. Robustness of UV spectrophotometer analytical method was determined by analyzing the 15 µg/ml LFD solutions at different wavelengths *i.e.* 286 ± 15 nm and temperatures *i.e.* 25±20°C (% RSD limit: < 2%) (Christian *et al*., 2017; Sarkar *et al.,* 2006; Silva-Buzanello *et al.,* 2015).

Statistical analysis

Linear regression of calibration curve was assessed using GraphPad Prism v6.01 for windows (GraphPad Software, San Diego California, USA). Statistical difference (*P < 0.05) was considered significant.

Results and Discussions

Absorption maxima (λ_{max}) and calibration curve of LFD

Absorption Maxima (λ_{max}) of LFD acquired through UV scan of LFD (5 µg/ml) in PB-6.8 was found to be 286 nm. Calibration curve of LFD was acquired using UV spectrophotometer technique by plotting a graph between concentrations of LFD *vs.* absorbance value obtained at 286 nm (Figure 1). Statistical analysis of calibration curve was performed by curve linear regression. Regression coefficient and p-value was found 0.998 and < 0.0001, respectively, which illustrated goodness of fit as well as statistical significance of proposed method (Table 2) (Sharma *et al.,* 2017, Singh *et al.,* 2016).

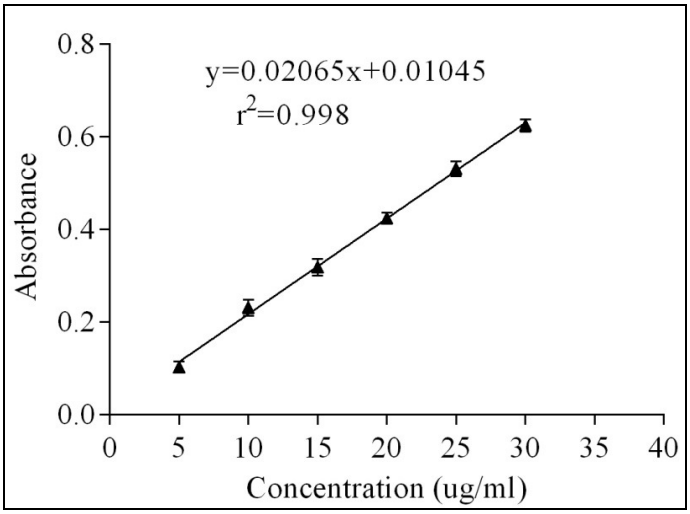

Fig. 1 : Standard curve for Lafutidine

Table 2 : Statistical data acquired by linear regression of LFD standard curve

Factor	Best-fit data	95% Confidence Intervals	Goodness of Fit
Slope	0.02065 ± 0.0004638	0.01936 to 0.02193	R^2 = 0.998
Y-intercept when X=0.0	0.01045 ± 0.009031	-0.01462 to 0.03552	P-value = < 0.0001
X-intercept when Y=0.0	-0.5060	-1.823 to 0.6708	

Linearity

The linearity range for LFD at 286 nm was found 5-30 µg/ml which has been confirmed by regression coefficient value of 0.9974 (n=3) (Figure 2) (Sarkar *et al.,* 2006; Silva-Buzanello *et al.,* 2015; Miller *et al.,* 2005). LOD and LOQ of the proposed UV method were found 1.96 and 5.96 µg/ml, respectively which illustrated high sensitivity of developed analytical method.

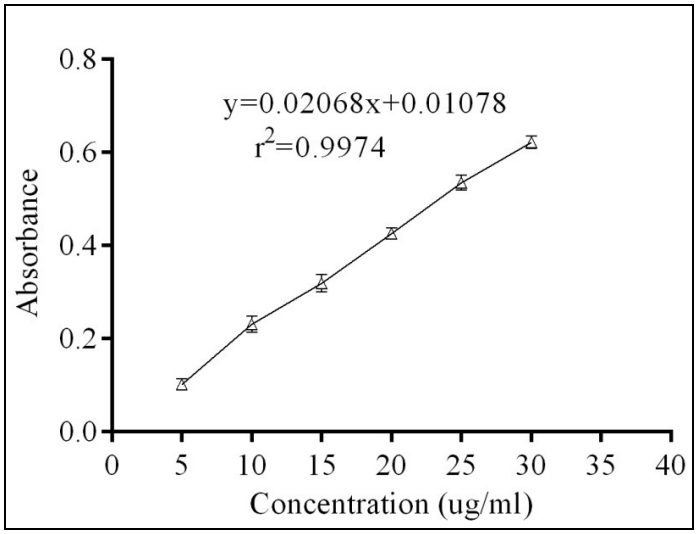

Fig. 2 : Graphical representation of linearity

Accuracy

Accuracy validation of UV spectrophotometer analytical method was performed by spiking method. Accuracy of an analytical process articulates the proximity of agreement among spiked and recovered amount using UV spectrophotometer analytical procedure (R^2 = 0.999) (Figure 3). The accuracy was determined as percentage drug recovery from 10, 15 and 20 µg/ml LFD. The percentage mean recovery of LFD was found 101.27 % (Table 3). Average percentage recovery of LFD was 101.49% which lies in acceptable limits of mean percentage recovery are 98%-102% with % RSD value 0.45 (< 2%) which indicated good accuracy (Davidson *et al.,* 2002; Sarkar *et al.,* 2006; Silva-Buzanello *et al.,* 2015).

Table 3 : Accuracy determination of UV-spectrophotometer analytical method

Amount added	Recovered	% Recovered	Statistical analysis
10	10.9	101.5	Mean = 101.27 % SD = 0.455 % RSD = 0.45
15	15.1	101.57	
20	20.6	100.75	

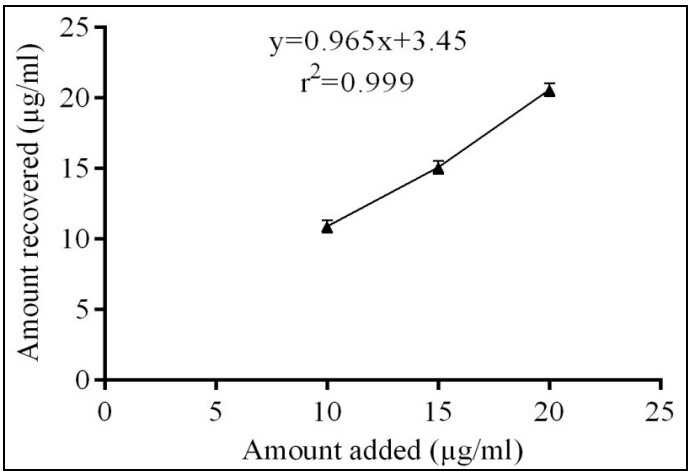

Fig. 3 : Graphical illustration of accuracy

Specificity

Specificity of UV spectrophotometer analytical method was determined by analyzing LFD in presence and absence of excipients (Poloxamer 407 and PVP K-30). Mean recovery of LFD was found 100.57% which was within accepted limit (98-102 %). The % RSD was found 0.70% (< 2%) which validated specificity of analytical method (Table 4) (Abdelwahab *et al.,* 2012; Maleque *et al.,* 2012; Divya *et al.,* 2014).

Table 4 : Specificity determination of UV-spectrophotometer analytical procedure

Poloxamer 407: PVP K30 (1:1)	LFD input (mg)	LFD Recovered (mg)	LFD Recovered (%)	Mean Recovered	Statistical Analysis
100 %	20	20.7	100.87	100.57 %	Mean = 100.57 % SD= 0.700407 % RSD = 0.70
200 %	20	20.2	100.25		
300 %	20	19.7	99.62		
400 %	20	20.2	101.5		
500 %	20	20.5	100.62		

Repeatability (intra-day precision)

The % RSD for absorbance values of 10, 15 and 20 µg/ml LFD at three different time periods within a day was found to be 2.08%, 1.33% and 18.67% (Table 5) (Alamri *et al.,* 2016; Divya *et al.,* 2013; Prashant *et al.,* 2013; Sarkar et al., 2006).

Table 5 : Measurement of Repeatability for 3 different concentrations of LFD

Conc (µg/ml)	Absorbance			Average	S.D	% RSD
10	0.231	0.232	0.233	0.232	0.001	0.43%
15	0.317	0.314	0.315	0.315	0.0015	0.48%
20	0.424	0.422	0.421	0.422	0.0015	0.36%

Intermediate Precision

The % RSD for absorbance values of 10, 15 and 20 µg/ml LFD on three different days (inter-day) was found 1.25, 1.07 and 0.99 % (Table 6) (Breier *et al.,* 2007; Jain *et al.,* 2013; Silva-Buzanello *et al.,* 2015).

Table 6 : Inter-day precision determined for LFD.

Concentration (µg/ml)	Days			Average	S.D	% RSD
10	0.230	0.232	0.234	0.232	0.002	0.86%
15	0.316	0.314	0.317	0.315	0.00152	0.48%
20	0.423	0.424	0.426	0.424	0.00152	0.36%

% RSD of absorbance values of 15 µg/ml LFD analyzed through dissimilar equipments and analysts was found < 2% which showed intermediate precision of analytical technique (Table 7).

Table 7. Intermediate precision determined for LFD (*n*=6).

Condition	Trials	Absorbance	Mean	SD	%RSD
Analyst-1	1	0.423	0.422	0.0018	0.44%
	2	0.421			
	3	0.425			
	4	0.424			
	5	0.422			
	6	0.420			
Analyst-2	1	0.421	0.422	0.0023	0.55%
	2	0.420			
	3	0.426			
	4	0.425			
	5	0.423			
	6	0.422			

Equipment-1	1 2 3 4 5 6	0.420 0.427 0.424 0.426 0.423 0.425	0.424	0.0024	0.59%
Equipment-2	1 2 3 4 5 6	0.427 0.424 0.426 0.423 0.425 0.422	0.424	0.00187	0.44%

Robustness

% RSD of absorbance values of sample solutions analyzed at different wavelengths and temperatures was found 1.48 and 1.73%, respectively (% RSD < 2%) which validated robustness (Christian *et al.,* 2017; Sharma *et al.,* 2017, Singh *et al.,* 2016; Silva-Buzanello et al., 2015) (Table 8).

Table 8 : Robustness studies of UV spectrophotometer analytical method.

Condition	Parameter	Absorbance	Mean	SD	% RSD
Change in Wavelength	275 nm	0.423	0.423	0.002	0.47
	290 nm	0.425			
	305 nm	0.421			
Change in temperature	5°C	0.423	0.4233	0.00152	0.36
	25°C	0.425			
	45°C	0.422			

Tabular Summary of validation parameters

Results of validation parameters of UV spectrophotometer analytical method for LFD has been summarized in Table 9.

Table 9 : Validation parameters of UV-spectrophotometer analytical method

Parameter	Result
λ_{max} (nm)	286
Regression equation (y= mx + c)	Y=0.02065x+0.01045
Regression coefficient (r^2)	R^2 = 0.998
Linearity (r^2)	0.9974
Accuracy	0.45 (% RSD)
Specificity	0.70 (% RSD)
Repeatability indicated by % RSD for LFD (10, 15 and 20 µg/ml)	10 µg/ml = 0.43% 15 µg/ml = 0.48% 20 µg/ml = 0.36%
Intermediate precision indicated by % RSD (Day-1, Day-2, Day-3)	Day 1 = 0.86% Day 2 = 0.48% Day 3 = 0.36%
Intermediate precision indicated by % RSD (Analyst-1, Analyst-2)	Analyst 1 = 0.44% Analyst 2 = 0.55%
Intermediate precision indicated by % RSD (Equipment-1, Equipment-2)	Equipment 1 = 0.59% Equipment 2 = 0.44%
Robustness indicated by % RSD (λ_{max}, 286± 15 nm)	0.47%
Robustness indicated by % RSD (Temp. 25± 20°C)	0.36%
Limit of detection (LOD)	1.96 µg/ml
Limit of quantitation (LOQ)	5.96 µg/ml

Conclusion

The proposed spectrophotometer analytical method for determination of LFD was found straightforward, specific, accurate, precise and cost-effective. It was concluded that developed method was robust and negligibly affected by smaller variations in temperature and wavelength. Furthermore, analytical method was highly sensitive. Results from the method validation illustrated reliability as well consistency pertaining to analytical results of LFD and therefore, proposed analytical technique could be an integral part of further evaluation and characterization of prepared LFD-SND.

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Conflict of Interest

The authors declare no conflict of interest.

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